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## Reflections on the Sulphonylurea Story. A Drug Class at Risk of Extinction?

Cordiner, Ruth L. M.; Pearson, Ewan R.

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Authors

**Cordiner RLM**

**Pearson ER**

Address for Correspondence

Professor Ewan Pearson

Population Health & Genomics

School of Medicine

Level 5, Ninewells Hospital & Medical School

Dundee

DD1 9SY

+44 1382 383387

[e.z.pearson@dundee.ac.uk](mailto:e.z.pearson@dundee.ac.uk)

Sulphonylureas (SU) were discovered in 1942 when French researchers observed severe hypoglycaemia in patients receiving sulphonamide treatment for typhoid fever<sup>1</sup>. It was recognised that sulphonamide-induced hypoglycaemia mimicked the action of insulin<sup>2 3</sup>. SU were introduced to clinical practice in the 1950s.

The last 10 years have seen major advances in type 2 diabetes mellitus (T2DM) pharmacotherapy<sup>4 5 6</sup>. Such are these advances, that debate has been provoked that SU are no longer a justified second line therapy due to their inconsistent CV and mortality data<sup>7 8</sup>, risks of hypoglycaemia, weight gain and secondary failure<sup>9 10</sup>. By 2013, SU prescribing as add-on to metformin had fallen to 41.4% (95% CI 41.1% to 41.7%)<sup>11</sup> with new favour towards DPP-IV inhibitors. Notably, this was before prescribing prevalence of GLP1-RA and SGLT-2 inhibitors started to increase<sup>12 13</sup>.

The controversies regarding whether SUs should continue to be used second line in T2DM treatment have been heavily debated<sup>14</sup>, including at The American Diabetes Association annual scientific sessions in 2015<sup>15 16</sup>. It is hoped that the results of the CAROLINA cardiovascular outcome trial (CVOT) of linagliptin vs glimepiride, expected in 2019, will resolve some of the debated issues<sup>17</sup>.

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This article explores the beta-cell physiology underpinning mechanisms of action of SUs, examines their evidence base, and seeks answers for concerns over their place in modern-day practice. Do they have potential for re-branding? With insights into SU physiology, pharmacogenetics and CVOT, are some SUs more favourable than others?

### Reflections on Beta Cell Physiology & Sulphonylurea Pharmacokinetics

Several SU were available by the 1960s and were classified into two “generations”. First generation SU such as tolbutamide and chlorpropamide are now rarely used. Second generation SUs such as gliclazide (unavailable in USA), glipizide, glibenclamide (aka. glyburide) and glimepiride, are now some of the most widely prescribed drugs for T2DM (Table 1).

SU were identified to cause beta-cell depolarisation in the 1960s<sup>18</sup>, it was later noted that this was due to a decrease in the potassium permeability of the beta-cell membrane<sup>19</sup>. Patch clamp electrophysiology studies found SU interact with, and close ATP-sensitive potassium ( $K_{ATP}$ ) channels<sup>20</sup>.  $K_{ATP}$  channel closure decreases the permeability of the beta-cell membrane to potassium ions, which depolarises the membrane<sup>21</sup>.

SU, unlike glucose, inhibit the  $K_{ATP}$  channel directly, causing depolarisation through  $Ca^{2+}$  influx, resulting in glucose-independent insulin secretion<sup>22</sup>. Importantly, this differentiates SU from newer therapies (GLP-1RA and DPP4i) that work in a glucose-dependent manner. Along with this “first phase” of insulin secretion, SU also induce the later “second phase” of insulin secretion to induce continuous formation of insulin granules<sup>23</sup>.

The  $K_{ATP}$  channel consists of four sulphonylurea receptors (SUR) surrounding four pore-forming Kir6.x subunits, which belong to the ATP-binding cassette transporter family and were cloned in the late 1990s and early 2000s<sup>24</sup>. SUR are made up of 17 transmembrane helices and two intracellular nucleotide-binding domains for ATP-binding and hydrolysis<sup>24</sup>.

Tissue-specific  $K_{ATP}$  channels subunits are coded by different genes, which translate to Kir 6.1 and 6.2 protein subunits<sup>25</sup>. In addition, channel tissue variation is provided by alteration in the combination of Kir6.x and SUR subunits: pancreatic beta-cells carry Kir6.2/SUR1, cardiac muscle Kir6.2/SUR2A and SUR2B with either Kir6.1 or Kir6.2 is present in vascular smooth muscle<sup>26 27</sup>.

Gribble, Ashcroft and colleagues identified in *Xenopus* oocytes that the binding sites for SU with  $K_{ATP}$  channels are found on the SUR subunits, therefore different SU types will interact with the different  $K_{ATP}$  channels with different affinity<sup>28 29 30 31</sup>. The dose-response curve for SUR1 and SUR2 shows high and low affinity components of inhibition<sup>29</sup>. Gliclazide, glipizide, tolbutamide and mitiglinide inhibit Kir6.2/SUR1 with high affinity, but low affinity for Kir6.2/SUR2<sup>32</sup>. (Table 1) Whereas glibenclamide, glimepiride, meglitinide, and repaglinide block both Kir6.2/SUR1 and Kir6.2/SUR2 with high affinity<sup>28 31</sup>. Binding inhibition by gliclazide, glimepiride and repaglinide to Kir6.2/SUR1 is rapidly reversible, unlike

glibenclamide, glimepiride and meglitinide to Kir6.2/SUR2<sup>33</sup>. Subunit binding affinity and reversibility may therefore be crucial when addressing SU efficacy, failure and CV safety.

#### Could Insight from Sulphonylurea Studies in Neonatal Diabetes be Extrapolated to T2DM?

Studies in neonatal diabetes (NDM) have provided insight into  $K_{ATP}$  channel physiology, as approximately 50% of cases are caused by activating mutations in Kir6.2 (KCNJ11) or SUR1 (ABCC8)<sup>34 35 36</sup>. These mutations reduce the ability of ATP to close the  $K_{ATP}$  channel<sup>35</sup>, thus prevent glucose-induced depolarisation and insulin release.

NDM management advanced following a pharmacogenetic study of patients with Kir6.2 mutations. Of the 49 participants, 44 successfully switched from insulin to a high dose SU<sup>37</sup>. Switch was achieved with no episodes of severe hypoglycaemia, no increase in mild-to-moderate hypoglycaemia and was regardless of SU used<sup>37</sup>.

Physiological studies undertaken, before- and after introduction of SU in patients with activating  $K_{ATP}$  channel mutations were striking (Figure 1). Patients had no insulin secretory response to I.V. glucose or glucagon before transition off insulin. However, following established SU use, there was a large insulin secretory response to glucagon. Similarly, in SU patients, insulin secretion following an oral glucose or mixed meal stimulus was much greater than seen with IV glucose.

These results demonstrate that in patients with Kir6.2 mutations, the glycaemic benefit of SU resulting in near normoglycaemia and insulin cessation, is not due to a direct stimulatory effect of SU on insulin secretion, but due to SU raising the resting membrane potential of beta-cells to enable amplifying pathways to operate. Most patients with NDM have an HbA1c close to or within the non-diabetic range yet do not have hypoglycaemia, consistent with the SU treatment in these patients enabling glucose stimulated insulin secretion.

Could these insights be extrapolated to T2DM? NDM is a purely beta-cell disease, whereas T2DM physiology is multifactorial, influenced by insulin resistance, hyperglucagonaemia and impaired incretin effect. However, variants in SUR1 are also noted in adult diabetes; some present with impaired glucose tolerance, others with maturity-onset diabetes of the young (MODY), and others with T2DM<sup>38 39</sup>. A 40% reduction in glucose-stimulated insulin secretion (GSIS) in people with normal glucose tolerance is seen with a common variant of Kir6.2 (E23K)<sup>34 40</sup>; this mutation is associated with increased risk of T2DM. It is debated whether Kir6.2 (E23K) causes a reduction in ATP-inhibition<sup>41 40</sup>. Others postulate that the polymorphism in SUR1 (A1369S), which is linked to Kir6.2 (E23K) drives lower ATP-sensitivity<sup>42</sup>. Therefore, for at least some patients with diabetes,  $K_{ATP}$  channel dysfunction contributes to their diabetes aetiology, and these patients may have a relatively hyperpolarised beta-cell. The parallels here with NDM are apparent, suggesting that an appropriate dose of SU may promote GSIS with minimal hypoglycaemia.

## Is There a Role for Low Dose Sulphonylureas?

Henquin described a “sigmoidal hierarchy” between two pathways of GSIS<sup>43</sup>. Firstly, in the direct/triggering pathway whereby SU bind to SUR of the  $K_{ATP}$  channel and bring about channel closure. This stimulates insulin secretion and in-vitro stimulates insulin secretion in a glucose-independent mechanism. Secondly, the amplifying/potentiating pathway, in which incretin hormones (GLP-1/GIP), glucagon or arginine act to augment insulin secretion via a rise in cyclic AMP<sup>43</sup>.

In patients with T2DM, as is clearly seen in any study of conventional therapeutic dose of SU, this insulin secretion is not entirely glucose-regulated and there is a risk of hypoglycaemia. One can hypothesise that a low dose SU should potentiate beta-cell insulin secretion in a glucose-dependent mechanism. If true, their effect would raise the beta-cell membrane potential and, through “sigmoidal hierarchy”, allow activation of the amplifying pathway by glucagon and incretin hormones.

A study of an isolated rat pancreas showed that gliclazide at concentrations  $1/10^{\text{th}}$  of those deemed therapeutic (0.25mcg/ml) potentiated GSIS, without increasing fasting insulin<sup>44</sup>. Similarly, a study on just 20mcg/kg body weight of glibenclamide in normoglycemic patients had no effect on fasting insulin secretion<sup>45</sup>. Thus, if a suitably low dose is given, then partial  $K_{ATP}$  channel closure will result, the amplifying pathway will be augmented, and GSIS will occur. Interestingly, in a study of single dose vildagliptin and 5mg glibenclamide, the insulin secretion was increased following oral glucose but there was no greater risk of hypoglycaemia, consistent with glucose regulation of the combined treatment in this study where the OGTT was done just 30 minutes after the glibenclamide dose (i.e. concentrations would have been sub-therapeutic)<sup>46</sup>.

Studies suggest that there is minimal glycaemic benefit of successive dose-escalation of SU. A prospective, case-controlled dose-escalation study of gliclazide assessed the relationship between dose and fasting and post-prandial glucose<sup>47</sup>. In 13 patients, dose-escalation from 40mg to 80mg daily was associated with a significant change in mean blood glucose (mean [SD, 11.3 [4.2] vs 10.0 [3.9] mmol/L ( $p<0.001$ )) but not post-prandial excursion. Further dose-escalation from 80 to 160mg was not associated with additional clinical benefit. Significant change was only observed in 6hr post-prandial blood glucose (9.5 [4.2] vs 10.3 [4.1] mmol/L [171.1 (75.7) vs 185.6 (73.9) mg/Dl];  $p=0.018$ ).

Stenman et al drew similar conclusions: increasing the dose of glipizide to more than 10mg daily showed little glycaemic benefit in a cohort of 23 patients<sup>48</sup>. Patients were given glipizide in three different dose schedules (10mg once or twice daily or 20mg twice daily), observing that mean blood glucose on home-

monitoring was 12.4mmol/L during placebo versus 9.6, 9.2 and 8.9mmol/L respectively. The insulin response to a meal test was greatest after 10mg glipizide and weakest after 40mg ( $P = 0.02$ ).

Slow release formulations of glipizide and gliclazide result in lower, more sustained concentrations of sulphonylureas. For example, standard release glipizide has a statistically higher  $C_{max}$  of 1003 ng/ml lasting 1 – 8 hours, and may be given twice daily, whereas extended-release glipizide has a  $C_{max}$  of 499ng/ml lasting 6 – 12 hours<sup>49 50</sup>. In keeping with our hypothesis that lower dosing of sulphonylureas may be beneficial by enabling incretin action with minimal insulin secretion, modified-release gliclazide or glipizide are associated with low hypoglycaemic risk versus their short acting preparations such as glibenclamide/glyburide<sup>Error! Bookmark not defined.</sup> or glimepiride<sup>51</sup>, or the difference in SU-associated weight gain, and faster time-to-failure with glibenclamide ( $C_{max}$  97.2 -105 ng/ml after 2 hours<sup>52</sup>) than chlorpropamide ( $C_{max}$  22.7 – 26.8ug/ml sustained from 3 hours)<sup>53</sup>.

What is the mechanism of sulphonylurea failure? Are some sulphonylureas better than others?

Concern was raised as to the numbers of patients progressing to additional therapy following long-term SU treatment<sup>54</sup>. Although UKPDS did not show more rapid failure with SU compared to metformin, the ADOPT study does suggest that SU fail quicker than metformin and rosiglitazone<sup>10</sup>. Kaplan–Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. Notably, the ADOPT study assessed newly-diagnosed diabetics, with more residual beta cell function than established T2DM. Progression-to-failure may be provoked by SU-associated weight gain and fear of hypoglycaemia, leading to non-compliance, however several hypotheses exist for the molecular mechanism of failure.

Firstly, persistent SU closure of the  $K_{ATP}$  channels may result in beta-cell apoptosis; this was investigated in cultured human islets<sup>55</sup>. Glibenclamide (0.1 and 10 micromol) exposure for 4 hours induced 2.09- and 2.46- fold increase in beta-cell apoptosis. Repaglinide (0.01 and 1 micromol) exposure produced no change in beta-cell apoptosis. Low dose nateglinide (10micromol) did not induce beta-cell apoptosis, however a 1.49 increase in apoptosis was seen with higher concentration (1000 micromol).

Another hypothesis is that persistent closure of the  $K_{ATP}$  channels results in insulin secretory failure without beta-cell death. Slow-release glibenclamide pellets were implanted into wild-type mice to induce chronic  $K_{ATP}$  channel closure. The mice became progressively and persistently diabetic, with reduced insulin secretion in response to hyperglycaemia ( $p<0.05$ ). Within 1 week of treatment, wild-type mice had developed almost the same degree of glucose intolerance as  $K_{ATP}$  knockout mice. Interestingly, secretory capacity of wild-type mouse islets was restored within hours of glibenclamide washout, and in-vivo within

1 month after treatment termination. Immunostaining showed normal islet size and alpha/beta cell distribution within the islet, and no evidence of apoptosis. This study may give insight into secondary failure of SU treatment in humans with T2DM. Further studies are required, for example assessing whether insulin secretion can be restored after a SU treatment break.

Initial SU response and subsequent failure is highly variable. The UK Prospective Diabetes Study Group (UKPDS) examined SU failure in non-insulin dependent diabetic patients over 6 years<sup>56</sup>. They prospectively followed newly-diagnosed T2DM (n=1305) randomly allocated to chlorpropamide or glibenclamide. By 6 years, 44% had required additional therapy; 48% of those allocated to glibenclamide and 40% on chlorpropamide (p<0.01). Modelling of beta-cell function concluded those with lower function were more likely to fail (p<0.0001). SU failure rate was dependent on the phenotype at presentation; higher glucose concentrations at initial presentation, younger age of presentation, lower residual beta cell reserve and BMI <30.

Gliclazide was shown to cause less secondary beta cell failure than glibenclamide/glyburide (P<0.001)<sup>57</sup>. This could be explained by its reversible binding to the K<sub>ATP</sub> channel, and therefore it may not hyper-excite and exhaust beta-cells to the same degree as glibenclamide. There are three other potential explanations for this. The first relates anti-oxidant activity; that gliclazide has potent free radical-scavenging activity mediated by an azabicyclo-octyl ring on the SU core<sup>58</sup>. The second is that chronic hyperglycaemia may induce oxidative stress, reduction in beta cell mass and tissue damage<sup>59</sup>. Hyperglycaemia induces mitochondrial superoxide production, activating the uncoupling of protein 2, decreasing the ATP:ADP, producing an overall reduction in insulin secretion<sup>60</sup>.

Harrower concluded that gliclazide is the most potent SU with the lowest incidence of hypoglycaemia and reduced secondary failure rates<sup>61 62</sup>. He compared T2DM (n=112) concurrently treated with different SU for 1 year (chlorpropamide, glipizide, gliquidone, glibenclamide (glyburide) or gliclazide). Gliclazide and glibenclamide achieved best results in terms of normalisation of HbA1c (80% and 74% respectively). Secondary failure rates were analysed in T2DM (n=248) treated for 5 years with gliclazide, glibenclamide or glipizide. Gliclazide had the lowest secondary failure rate (7% in 5 years) and was significantly better than glipizide (25.6%) and just below significant threshold in comparison to glibenclamide (17.9%)<sup>62</sup>. In alternative methodology, UKPDS utilised a “coefficient of failure” chlorpropamide patients showed a mean COF of 0.34 HbA1c%/year (0.44%/year SD) and glibenclamide-treated patients 0.50 HbA1c%/year (0.50%/year SD) (p=0.046; unpaired two-tailed t-test)<sup>63</sup>.

## Can precision medicine modernise how we use sulphonylureas?

Pharmacogenetic variants have been associated with SU response or failure. In the  $K_{ATP}$  channel, Feng et al identified an association between carriers of risk A allele at Ala1369Ser of the ATP-binding cassette subfamily member gene ABCC8 (who have lower insulin secretory function)<sup>64</sup>, who had a greater decrease in fasting plasma glucose (FPG) and HbA1c after 8 weeks treatment with gliclazide. The GoDARTS study reported that loss-of-function CYP2C9 variants improve therapeutic response to SU in T2DM and were associated with less SU failure<sup>65</sup>. Incident users of SU in Tayside (n=1073) were assessed for the impact of the combined CYP2C9\*2 and CYP2C9\*3 genotypes on early and sustained SU response. Patients with two copies of a loss-of-function allele were 3.4 times ( $P = 0.0009$ ) more likely to achieve a treatment HbA1c level  $<7\%$  than patients with two wild-type CYP2C9 alleles. This was noted to correspond with a 0.5% ( $P = 0.003$ ) greater reduction in HbA1c. As mentioned, \*2 and \*3 allele carriers were less likely to experience treatment failure with SU monotherapy ( $P = 0.04$ ; per-allele HR 0.79; 95% CI 0.63-0.99). Further studies are required to evaluate whether genotype at CYP2C9 or ABCC8 can be used to improve outcomes of patients treated with sulphonylureas.

### Sulphonylurea Efficacy and Safety

There is no doubt that SU are effective, both in terms of initial HbA1c reduction and cost. A systematic review and meta-analysis of SU efficacy on HbA1c reduction, evaluated 31 trials with a median duration of 16 weeks<sup>66</sup>. SU monotherapy lowered HbA1c by 1.51% (17mmol/mol) more than placebo (95% CI 1.25, 1.78) (Figure 2). SU added to oral diabetes treatment lowered HbA1c by 1.62% (18mmol/mol; 95% CI 1.0, 2.24) compared with other therapy and SU added to insulin lowered HbA1c by 0.46% (6mmol/mol; 95% CI 0.24, 0.69) and lowered insulin dose. Higher SU doses did not produce any greater HbA1c reduction than lower doses. SU treatment resulted in more hypoglycaemic events (RR 2.41, 95% CI 1.41, 4.10) but did not significantly affect the number of adverse events. The ADOPT study compared SU versus metformin and rosiglitazone; SU showed greater HbA1C reduction in the first 6 months of treatment<sup>10</sup>. However, SU treatment failure was the highest versus comparators by end of study<sup>67</sup>. A recent re-analysis of the ADOPT study by the MASTERMIND consortium showed how SU were much more effective than Rosiglitazone in non-obese men. In contrast, obese women responded better over 5 years to Rosiglitazone than SU<sup>68</sup>.

A large meta-analysis addressed gliclazide efficacy and safety<sup>69</sup>, T2DM patients treated with gliclazide (n=3083) versus other OHA (n=3155) of at least 12-weeks duration were included. Outcomes were HbA1c change, severe hypoglycaemia incidence, weight change and mortality. Gliclazide was slightly more effective versus other OHA, apart from metformin (-0.13% (95% CI: -0.25, -0.02,  $I^2$  55%)). One out of 2387 gliclazide patients experienced a severe hypoglycaemic event, whilst concomitantly on insulin. There were 25 non-severe hypoglycaemic events (2.2%) in 1152 gliclazide users and 22 events (1.8%) in 1163 users in the comparator group (risk ratio 1.09 (95% CI: 0.20, 5.78,  $I^2$  77%)).



A large Canadian multi-centre study (n=114 sites) found gliclazide to be safe, well tolerated and efficacious in most patients studied <sup>70</sup>. Gliclazide (80mg – 320mg daily) was given for three months T2DM patients (n=411) sub-optimally controlled with diet or monotherapy. A significant reduction was seen in fasting, 2-hour and HbA1c levels compared with baseline (P = 0.01). Adverse events, aside from hypoglycaemia, were recorded in 7.3% of patients and led to withdrawal of 1.2% of patients from study. Hypoglycaemic events were less frequently encountered than with previous monotherapy (P = 0.001). However, it is important to note that severe hypoglycaemic events requiring medical attention compose a small fraction compared with the number of severe hypoglycaemic events requiring third-party assistance in community, or mild-moderate lows, the majority of which go undocumented.

The ongoing Glycaemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) compares SU (glimepiride) to other contemporary 2<sup>nd</sup> line treatment 2<sup>nd</sup> line treatment (sitagliptin, liraglutide or basal insulin) in 5047 patients for up to 7 years. Hopefully this study will establish the position of sulphonylureas relative to other second line treatments. However, it should be noted that SGLT-2 inhibitors, now commonplace 2<sup>nd</sup> line therapy with excellent outcome data, are not included in this analysis. The primary outcome is time to primary failure (HbA1c  $\geq 7\%$ ) while receiving metformin (up to 2000mg per day) and the randomly assigned study medication by intention-to-treat. The secondary outcome is time to secondary failure (HbA1c  $> 7.5\%$ ). GRADE will record other attributes such as CV disease, safety, tolerability and cost-effectiveness, however it is not powered as a clinical outcomes study.

#### Exploring Sulphonylurea Cardiovascular Safety

Sulphonylureas have chequered cardiovascular outcomes, however, it is important to note that many early conclusions were derived from studies which were not originally powered to evaluate these outcomes. Thus, the detrimental results of studies may have been overstated. It is hoped that the results of CAROLINA CVOT which reports in 2019 and compares linagliptin with glimepiride will establish once and for all whether sulphonylureas (albeit glimepiride only) increase CV risk <sup>17</sup>; this follows on from CARMELINA CVOT which established the CV safety of linagliptin versus placebo <sup>71</sup>.

In the 1970s, the University Group Diabetes Program (UGDP) was the one of the first randomised trials in diabetes <sup>72 73 74</sup>. Patients (n=200) were randomised to insulin, tolbutamide or placebo (a phenformin arm was later added). The tolbutamide arm was stopped prematurely due to increased death rate (12.7% vs. 4.9% in the placebo group) causing the FDA to issue a black-box warning against SU <sup>75</sup>. Of note, tolbutamide also displayed increased risk of CV events compared with insulin therapy, which also causes

hypoglycaemia. However, UDGP design and conduct are still disputed, as the tolbutamide cohort had increased CV events by the study outset<sup>76</sup>.

The UKPDS provided clearer guidance<sup>77</sup> observing that reducing glucose exposure (HbA1c 7.0% versus 7.9% over median 10.0 years), with SU or insulin therapy, reduced the risk of “any diabetes related endpoint” by 12% and microvascular disease by 25%, with a 16% trend to a reduced risk of myocardial infarction (MI) (P=0.052). UKPDS displayed no increase in CV death, MI or sudden death with SU use. However, the study was not powered to evaluate these outcomes.

The TOSCA.IT primary prevention trial also provided reassuring evidence for CV safety of SU<sup>78</sup>, having compared long-term CV outcomes of two widely used, and affordable drugs in T2DM. Patients were randomised to pioglitazone (n=1535) or SU (=1493) (2% glibenclamide, 48% glimepiride, 50% gliclazide), 11% of participants had documented previous MACE prior to study start. The trial was stopped early on basis of futility analysis after median follow up of 57.3 months. Data showed SU to have similar CV event incidence to pioglitazone as add-on to metformin. The primary outcome of composite first occurrence of all-cause death, non-fatal MI, non-fatal stroke or urgent coronary revascularisation was observed in n=105 (1.5 per 100 person-years) in the pioglitazone group, versus n= 108 (1.5 per 100 person-years) on SU (HR 0.96, 95% CI 0.74-1.26, p=0.79). SU had increased reported hypoglycaemia than pioglitazone (508 (34%) vs 148 (10%), p<0.0001). The PROACTIVE study showed that pioglitazone reduced CV events (main secondary endpoint of all-cause mortality, non-fatal MI, and stroke) compared to placebo, the finding that patients randomised to SU had similar CV outcomes to those treated with pioglitazone in TOSCA.IT does suggest that SU do not increase CV events. However, it should be noted that PROACTIVE study was again not powered to assess CV safety as a primary endpoint and recruited a cohort of patients with established CV disease or high CV risk.

Large meta-analyses report inconsistent findings on SU CV safety, these can be divided into meta-analyses of randomised controlled trials (RCT), and meta-analyses of observational data<sup>79 80 81</sup>. A Cochrane meta-analysis of 72 RCT assessed the effects of SU monotherapy (n=9707) versus placebo, no intervention or other OHA (n=12,805). No significant association was found between SU and mortality versus metformin monotherapy (pooled RR 1.47, 95% CI 0.54 – 4.01). The meta-analysis showed that the impact of SU on CV safety may not be a class effect; first generation sulphonylureas were associated with increased CV mortality compared to placebo (RR 2.63, 95% CI 1.32 – 5.22, p = 0.006), whereas no difference was found with second generation sulphonylureas. It should be noted that none of the studies were powered to detect CV events<sup>81</sup>.

Observational studies tend to report increased CV risk for SU versus comparator (often metformin). It is difficult to draw conclusions from observational studies as there is scope for considerable bias, even after rigorous methods to account for this.

### Does Tissue Specificity of Sulphonylureas Affect Cardiovascular Safety?

A recent study used genetic variation in SUR to predict the causal association of  $K_{ATP}$  channel closure (mimicking SU action) on CHD outcomes<sup>82</sup>, the results are summarised in Figure 3. In 120,286 UK Biobank participants, the p.A1369S SUR1 variant described earlier was associated with a significantly lower risk of T2DM (odds ratio (OR) 0.93; 95% CI 0.91, 0.95;  $P=1.2 \times 10^{-11}$ ). Importantly, pA1369 was associated with a reduced risk of CV disease (OR 0.98; 95% CI 0.96, 0.99;  $P = 5.9 \times 10^{-4}$ ). The variant was associated with increased BMI (+0.062 kg/m<sup>2</sup>; 95% CI 0.037, 0.086;  $P = 8.1 \times 10^{-7}$ ) but lower waist-to-hip ratio adjusted for BMI. The data emphasises that SU may reduce the risk of CV disease, despite their association with weight gain.

In the SPREAD DIMCAD study, first generation sulphonylureas were associated with increased CV events. This may be due their lower affinity for pancreatic beta-cell SUR1, but higher affinity for cardiac and vascular smooth muscle SUR2 which may interfere with ischaemic cardiac pre-conditioning<sup>83</sup>. Second generation SU have an affinity for SUR1 with no effect on cardiac or vascular smooth muscle SU receptors<sup>84 85</sup>, which upholds the findings of Gribble et al.<sup>31</sup>. Non-selective blockade of myocardial SUR receptors worsens post-ischaemic wall function by shortening the action potential<sup>86 87 88</sup>.

A meta-analysis and systematic review addressed tissue-selectivity and mortality risk among SU<sup>89</sup> observing that gliclazide and glimepiride were associated with a lower risk of all-cause and CV-related mortality compared with glibenclamide. In contrast, a series of retrospective analyses by Pantalone et al<sup>90</sup> observed increased mortality risk of SU (glipizide, glyburide/glibenclamide, glimepiride) versus metformin<sup>91</sup>. Further analysis did not identify increased mortality risk among the different SU combinations and metformin<sup>92</sup>. In an additional retrospective analysis of the same SU as monotherapy, there was no increased mortality risk between individual SU however, glimepiride was the preferred SU in those with underlying CAD<sup>93</sup>. It should be noted that as this retrospective analysis was conducted in the USA, gliclazide was not part of the analysis. It should also be noted in contrast to gliclazide, that glimepiride is not pancreatic SUR selective (Table 1).

A retrospective cohort study (n=14,213) assessing the dose-response relationship between gliclazide, glibenclamide (glyburide) and MACE, demonstrated once again that low dose SU is better than high dose SU, and that SUs with pancreatic specificity are better than those without<sup>94</sup>. MACE was higher in both high-dose gliclazide and glibenclamide versus low-dose (gliclazide crude rates: 32.8 and 28.2 per 1000 person-

years, 1.15; 95% CI (0.96-1.38), glibenclamide crude rates: 38.9 and 31.5 per 1000 person-years; HR 1.24; 95% confidence interval 1.02-1.50)) (Figure 4). Furthermore, in patients who have had a myocardial infarction, Glibenclamide (glyburide) binding to SUR on cardiac myocytes may result in increased infarct size and reduced LV function<sup>95</sup>. This was similarly demonstrated in rat models comparing glibenclamide with gliclazide on myocardial infarct size<sup>95</sup>. Glibenclamide, but not gliclazide, was noted to exacerbate ischaemic/reperfusion injury along with associated with deterioration in LV function post-MI in diabetic hearts.

### Conclusion

Since the accidental discovery of the hypoglycaemic effect of sulphonamides over 60 years ago, SU have become a stalwart of T2DM management. Despite the increasing therapeutic options, SU still have an important role to play in glucose lowering therapy. We have highlighted how the concerns regarding hypoglycaemia, secondary failure and cardiovascular safety are over-stated. Especially when one considers the data for gliclazide rather than non-selective SU such as glibenclamide. As shown, the evidence not only suggests that gliclazide has efficacy in terms of glycaemic control<sup>55</sup>, lower secondary failure rates<sup>49</sup>, and is equivalent to pioglitazone in terms of incidence of CV events in the TOSCA.IT study<sup>69</sup>. Glipizide is probably the most selective SU and should be considered. However, as CV outcomes for glipizide are not well reported, evidence does not point to a clear alternative in the absence of gliclazide<sup>96</sup>.

We believe that the issues of hypoglycaemia and secondary failure may be minimised by considering the physiological action of SU, the insights gained from the treatment of patients with NDM, and the beneficial outcomes of slow release lower dose preparations of SU. These data suggest that SU are used in too high a dose, and lower doses of SU may be only slightly less effective yet have reduced risk of SU and secondary failure. With research into these areas it may be possible to modernise the use of this old drug class and prevent a useful drug class in the management of diabetes falling from use.

### Acknowledgements

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## Figure Legends

**Table 1. Summary of Commonly Used Sulphonylureas, SUR Affinity and Pharmacokinetics**

### **Figure 1. Physiological Studies of the Effect of Associated Mechanisms of Sulfonylurea Treatment on Insulin Secretion**

**Panel A** shows the median incremental increase in insulin concentration above baseline in an intravenous glucose-tolerance test (16 patients) and an oral glucose-tolerance test (5 patients) before treatment was switched from insulin to sulfonylureas (blue lines) and after treatment (black lines).

**Panel B** shows the median incremental increase in insulin and glucose concentration from baseline in response to intravenous glucose, oral glucose and mixed meal in seven patients whose treatment was successfully switched from insulin to sulfonylurea.

**Panel C** shows median concentration of total glucagon-like peptide 1 (GLP1) (blue lines) and the median incremental increase in insulin concentration above baseline (red lines) in response to an oral glucose-tolerance test in four patients before and after treatment was switched to sulphonylurea.

**Panel D** shows the median incremental increase in insulin concentration above baseline after glucagon stimulation in five.

**Figure 2. Reproduced from Hirst et al, Estimating the effect of sulphonylurea on HbA1c in diabetes: a systematic review and meta-analysis. Diabetologia May 2013, 56(5) pp973-984.** Mean difference in change in HbA1c of sulfonylurea monotherapy treatment vs placebo (boxes) and pooled estimates (diamonds) calculated by the random effects DerSimonian and Laird method. Horizontal bars and diamond widths denote 95% CIs and box sizes indicate relative weight in the analysis.

Permission Required Prior to Publication

**Figure 3. Reproduced from Emdin et al. Genetic Variation at the Sulphonylurea Receptor, Type 2 Diabetes and Coronary Heart Disease. Diabetes. 2017 Aug;66(8)2310-2315**

Permission Required Prior to Publication

- a) Association of ABCC\* p.A1369S with Type 2 Diabetes and Coronary Heart Disease
- b) Association of ABCC8 p.A1369S with Cardiometabolic Traits
- c) Association of ABCC8 p.A1369S with Cardiovascular Disease

### **Figure 4. Hazard ratios (HR) for major adverse cardiovascular events among new users of gliclazide and glyburide**

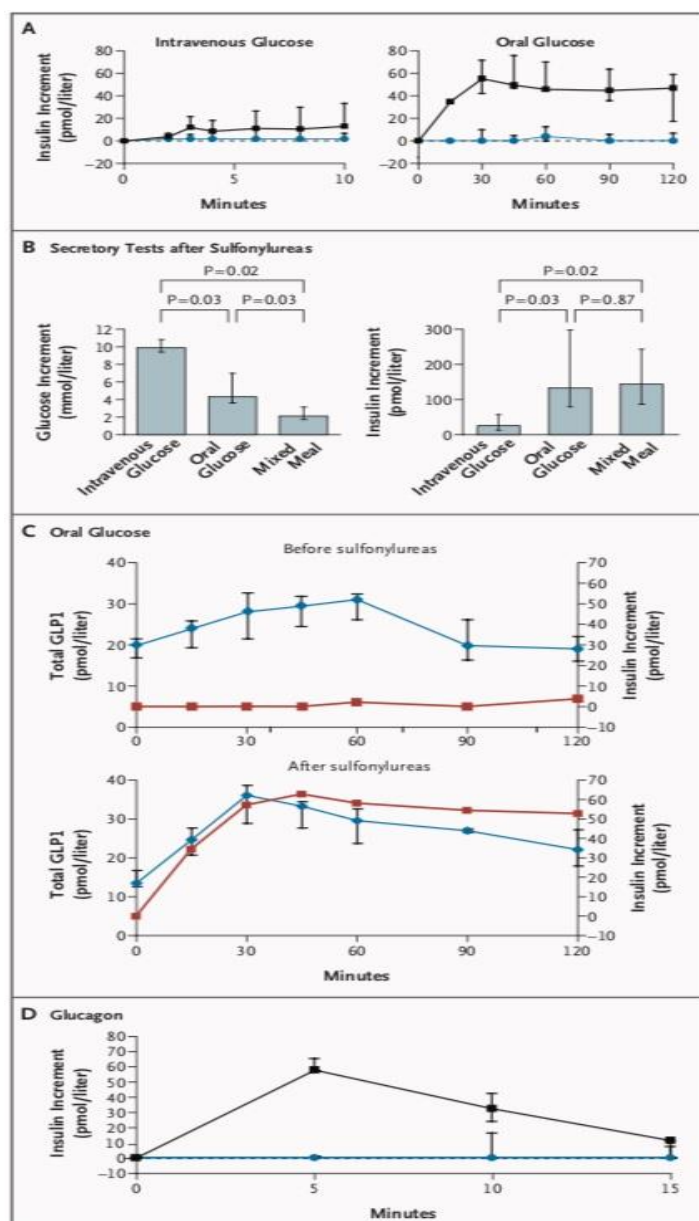
Adapted from Ahmed S, Abdelmoneim et al. Dose response relationship between sulfonylureas and major adverse cardiovascular events in elderly patients with type 2 diabetes. Pharmacoepidemiology and Drug Safety. 2016 Oct;25 (10):1186 – 1195.

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Table 1 – Commonly Used Sulphonylureas, SUR Affinity and Pharmacokinetics<sup>97 98 99</sup>

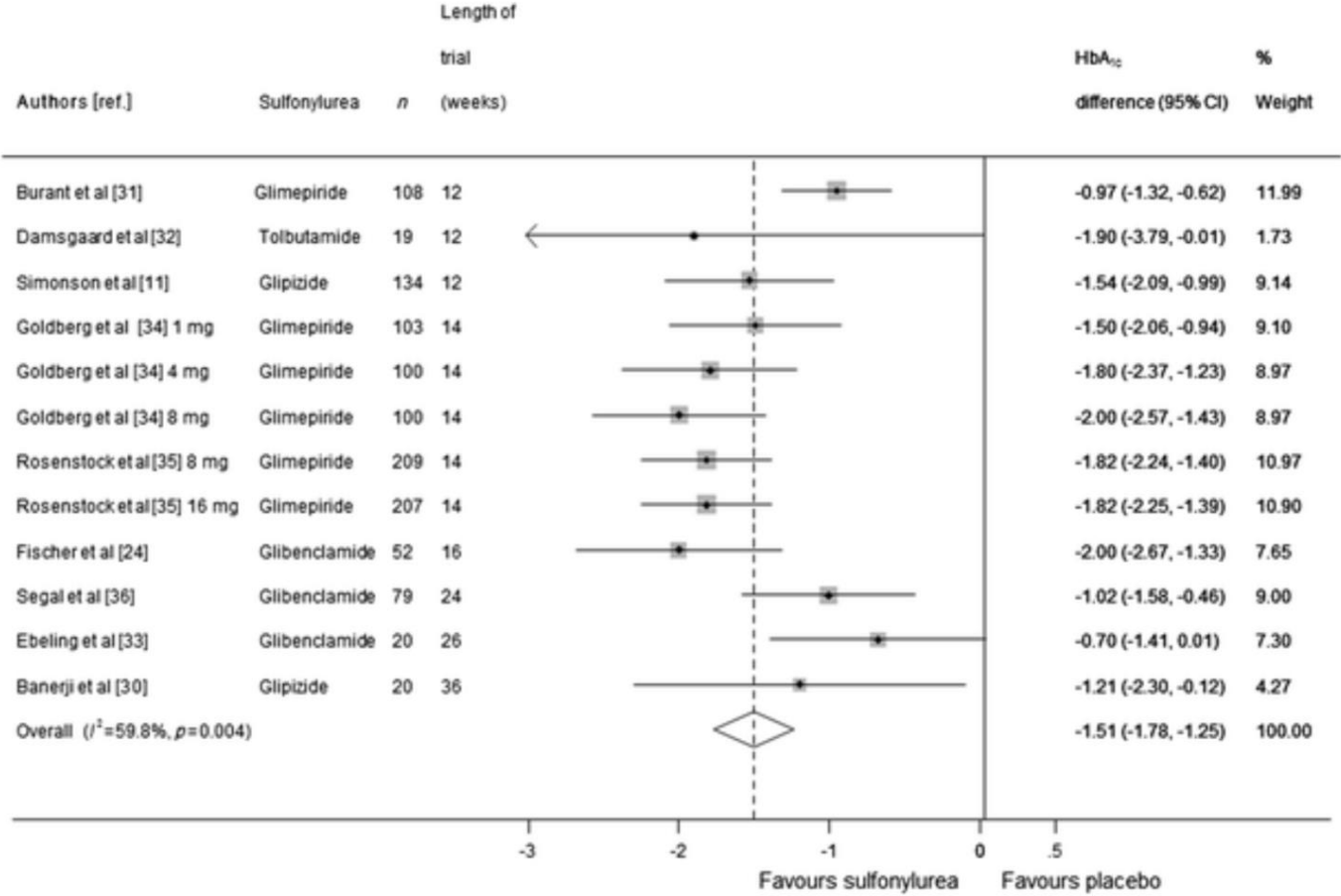
Sulphonylurea	Trade Name	Dose Range	SUR High Affinity	SUR Low Affinity	Onset	Peak Concentration	T $\frac{1}{2}$ Plasma
<b>First Generation</b>							
Tolbutamide	Tolbutamide	0.5 – 2g Daily	Kir6.2/SUR1	Kir6.2/SUR2	1 Hour	Serum: 3-4 Hours	4 – 25 Hours
Chlorpropamide	Diabinese	100 – 750mg Daily	Kir6.1/SUR1 Kir6.2/SUR2		1 Hour	Effect: 3 – 6 Hours Serum: 2-3 Hours	36 Hours
Tolazamide	Tolazamide	100mg – 1000mg Daily	Kir6.2/SUR1	Kir6.2/SUR2	20 Minutes	Effect: 4-6 Hours Serum: 3-4 Hours	7Hours
<b>Second Generation</b>							
Glibenclamide/ Glyburide	Daonil	5 – 15mg Daily	Kir6.1/SUR1 Kir6.2/SUR2		15 – 60 Minutes	Serum: 2-4 Hours	10 Hours
Gliclazide (Not available in USA)	Diamicron	40 – 320mg Daily	Kir6.2/SUR1	Kir6.2/SUR2	1 Hour	Serum: 1 – 8 Hours	6 – 14 Hours
	Diamicron MR (Modified Release)	30 – 120mg Daily				Modified Release: 6 – 12 Hours	16 Hours
Glipizide	Glibenese Minodiab	2.5 – 20mg Daily	Kir6.2/SUR1	Kir6.2/SUR2	15 – 30 Minutes	Serum: Immediate Release 1-3 Hours	2-5 Hours
	Glucotrol XL					GITS/Sustained Release 6 – 12 Hours	15 Hours
Glimepiride	Amaryl	1 – 6mg Daily	Kir6.1/SUR1 Kir6.2/SUR2		2 – 3 Hours	Serum:2-3 Hours	5 – 9 Hours

Figure 1



“From Ewan R. Pearson M.R.C.P, P.H.D et al. Switching from Insulin to Oral Sulfonylureas in Patients with Diabetes Due to Kir6.2 Mutations. New England Journal of Medicine 2006; Volume 355, Page 467 – 477”.  
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Figure 2



Sulphonylurea Monotherapy Trials



Figure 3

Outcome	Source	Case (n)	Control (n)	Odds Ratio for S Amino Acid	P value
Type 2 Diabetes	DIAGRAM + UKBB	40,581	221,578	0.93 [0.91; 0.95]	3.0*10 <sup>-11</sup>
Coronary Heart Disease	CARDIOGRAM Exome + UKBB	85,629	228,244	0.98 [0.96; 0.99]	5.9*10 <sup>-4</sup>

A) Association of ABCC8 p.A1369S with type 2 diabetes and coronary heart disease

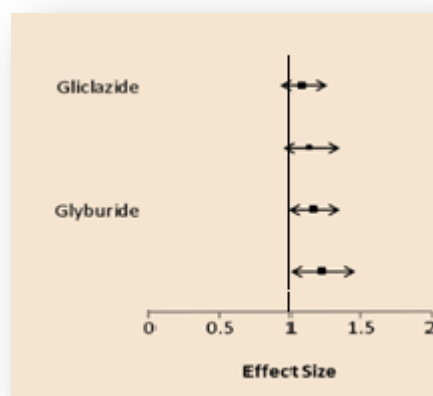
Trait	Source	N	Effect (SD) of S Amino Acid	Effect	P value
<b>Anthropometric</b>					
BMI (kg/m <sup>2</sup> )	GIANT+UK Biobank	436,729		0.062 [0.037, 0.086]	8.07*10 <sup>-7</sup>
Waist Circumference (cm)	GIANT+UK Biobank	346,934		0.083 [0.0095, 0.16]	0.027
Hip Circumference (cm)	GIANT+UK Biobank	327,872		0.095 [0.045, 0.15]	2.3*10 <sup>-4</sup>
Waist-to-Hip Ratio adj. BMI	GIANT+UK Biobank	324,419		-0.00093 [-0.0014, -0.00045]	1.6*10 <sup>-4</sup>
<b>Glycemic</b>					
Fasting Glucose (mg/dL)	MAGIC	133,010		0.033 [-0.024, 0.089]	0.26
Fasting Insulin (log transformed)	MAGIC	108,557		0.0028 [0.00057, 0.0051]	0.014
2-h Glucose	MAGIC	42,854		-0.29 [-0.51, -0.075]	0.0084
HbA <sub>1c</sub> (%)	MAGIC	46,368		-0.00069 [-0.0044, 0.0031]	0.72

B) Association of ABCC8 p.A1369S with cardiometabolic traits

Data Source	Source	Case (n)	Control (n)	Odds Ratio per S Amino Acid	P value
Coronary Heart Disease	CARDIOGRAM Exome + UKBB	85,629	228,244	0.98 [0.96; 0.99]	5.9*10 <sup>-4</sup>
Stroke	UKBB	2,218	118,068	0.97 [0.91; 1.03]	0.32
Heart Failure	UKBB	639	119,647	0.93 [0.83; 1.04]	0.19
Peripheral Vascular Disease	UKBB	752	119,534	0.94 [0.85; 1.05]	0.28
<b>Fixed-effects model</b>				0.97 [0.96; 0.99]	1.0*10 <sup>-4</sup>
Test for heterogeneity: P = 0.7401					

C) Association of ABCC8 p.A1369S with cardiovascular disease

Figure 4



	MACE n(per 1000 person years)		Hazard Ratio HR (95% Confidence Interval)
	Low Dose	High Dose	
Gliclazide	302 (29.2)	336 (32.2)	1.10 (0.94 – 1.29)
	206 (28.2)	288 (32.8)	1.15 (0.96 – 1.38)
Glyburide	278 (32.8)	326 (38.6)	1.18 (1.00 – 1.38)
	185 (31.5)	247 (38.9)	1.24 (1.02 – 1.50)

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